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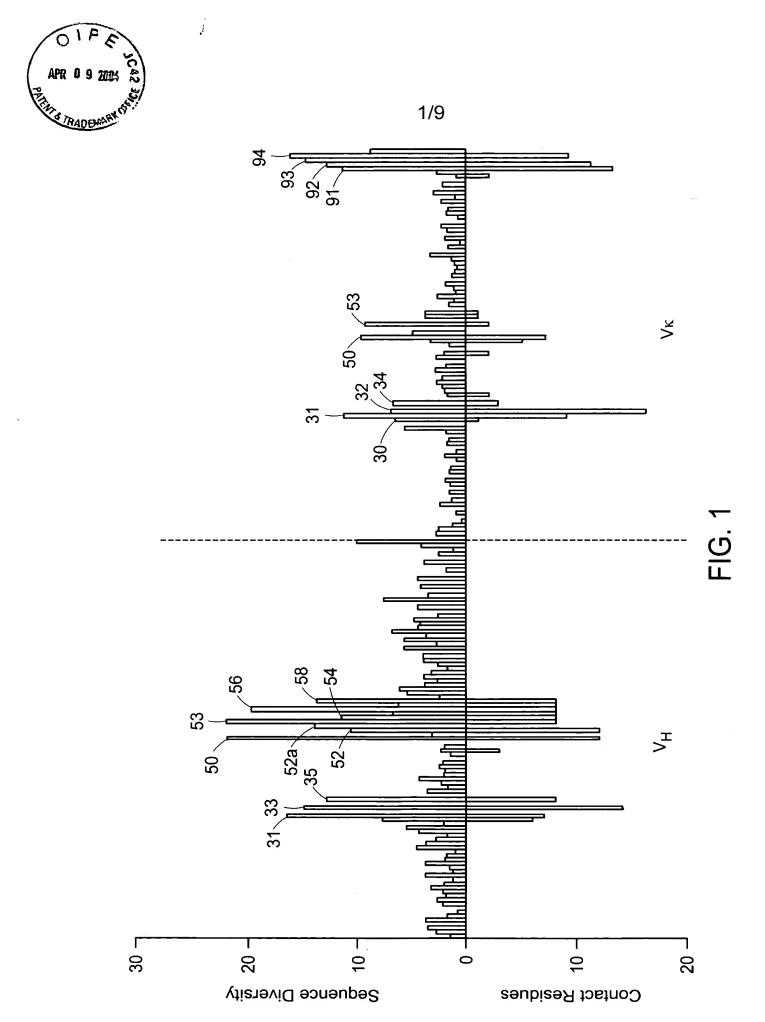
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S AGC ഥ G വ Ø c Ig ည် L CH H20 CTG AGA  $\alpha$ П വ TTG GTA CAG CCT GGG GGG Ç Ç о Р H10 G G G Œ

FIG. 2A

FIG. 2B

F G. 2

Ö H52 CGC CAG GCT CCA GGG AAG GGG CTG GAG TGG GTC TCA 四 SIC SIC

GAC TTC ACC ATC TCC AGA GAC AAT TCC AAG AAC ACG CTG TAT CTG CAA ATG AAC AGC CTG AGA GCC ഗ H70

H82

H80

H60

SS TAC TGG GGC CAG GGA ACC CTG GTC ACC GTC TCG AGC GGT GGA വ H110 GAC  $\Box$ H98 H100 [IL4 A



AGA വ G വ Ø L S CTG TCT ( လ 110 လ T D 口 လ 5 Ç Ŋ 5

ATC TTA AAT TGG TAT CAG CAG AAA CCA GGG AAA GCC CCT AAG L40 z Z S ഗ L30 LCDR1 വ ø L20

GGG ACA GAT TTC ACT CTC ACC ATC AGC  $\Box$ С TCT ഗ GGA G GGC AGT വ Ŋ GGG GTC CCA TCA AGG TTC AGT വ 24 ഗ > A S S L Q S GCA TCC AGT TTG CAA AGT CDR2 TAT

TIC GGC CAA GGG ACC AAG GTG GAA ATC AAA 1107 ₽ G Ŏ හ ᄄ ⊢ Z Д S Y S T AGT TAC AGT ACC CAA CCT GAA GAT TTT GCA ACT TAC TAC TGT CAA CAG ŏ ŏ Ω L90 Ø ᄄ  $\Box$ 压 പ

LCDR3

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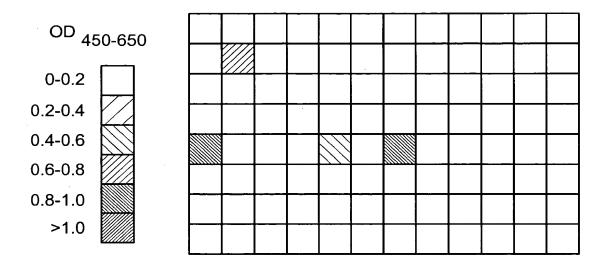
Diversified in "Primary" library only

Diversified in "Somatic" library only

Diversified in "Primary" and "Somatic" libraries



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"Primary" NNK library before pre-selection



"Primary" NNK library after pre-selection

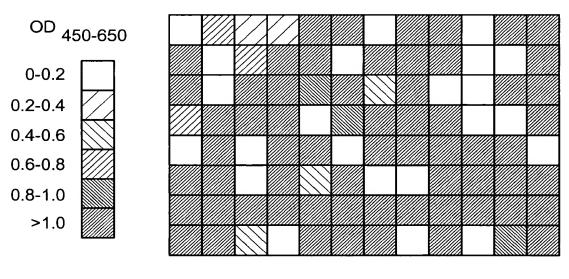


FIG. 3

FIG. 4B
FIG. 4C

FIG. 4



APT	15 A
	04UEAC

No*	9	9	2	$\leftarrow$	m	9	4		-	7	ч	Ч	7	$\leftarrow$	Н	3
CDR3	$\overline{QQS}\overline{SNT}\overline{PY}$ T	QQSYSTP <u>S</u> T	QQ <u>yrlr</u> p <u>l</u> t	Τ <u>νασλιγ</u> οο	QQ <u>GYNKPR</u> T	$\overline{Q}$	QQEKMVPLT		QQGQHRPLT	ı	ı	QQ <u>RAKK</u> P <u>P</u> T	$\overline{QQSYSTPHT}$	QQSYSTP <u>S</u> T	QQSYSTPLT	QQSYSTP <u>P</u> T
CDR2	<u>R</u> AS <u>S</u> LQS	AASSLQS	$\overline{\text{HASR}}$ LQS	$\underline{Y}AS\underline{H}LQS$	QASELQS	AASSLQS	$\overline{\mathtt{E}}\mathtt{AS}\overline{\mathtt{T}}\mathtt{LQS}$		HASITÕS	ı	ı	RASRLQS	AASSLQS	AASSLQS	AASSLQS	AASSLQS
CDR1	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN		RASQSISSYLN	ı		RASQSISSYLN	RASQSINENLS	RASQSI <u>FMR</u> LN	RASQSI $\underline{\text{STLLN}}$	RASQSI <u>GPF</u> L <u>S</u>
CDR3	GGSMFDY	KASSFDY	RAGI FDY	GGRLFDY	GSQAFDY	GTRRFDY	RDKLFDY		PSPPFDY	<u>OVSR</u> FDY	GRPRFDY	TNRSFDY	GRWPFDY	NEPRFDY	GYRKFDY	GYRKFDY
CDR2	<u>IIGSEGWP</u> T <u>I</u> YADSVKG	AISGSGGSTYYADSVKG	LISPLGKDTSYADSVKG	<u>GIRRVGQA</u> T <u>S</u> YADSVKG	<u>AINTKGMT</u> TDYADSVKG	AISGSGGSTYYADSVKG	<u>AISPKGRRTY</u> YADSVKG		RITPAGRRTTYADSVKG	RITPAGHRTYYADSVKG	<u>TISPQGLR</u> TTYADSVKG	<u>TISPKGRS</u> TŢYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG
CDR1	SYAMS	AYAMI	SYAMS	SYAMS	SYAMS	MYQMH	SYAMS		SYAMS	SYAMS	SYAMS	SYAMS	KYRME	RYRMH	RYRMG	RYRMG
Library	<i>Primary</i> NNK	SomaticNNK	PrimaryNNK	=	=	SomaticNNK	PrimaryNNK		11	=	=	±	SomaticNNK	11	"	=
Antigen	Bovine ubiquitin	=	RatBIP	=	E.	=	Bovine	Histone	#	=	=	=	11	=	=	=
Clones	UBIA 1-9	UBIB 1,3-10	BIPA1-3,6,9	BIPA4	BIPA5,7,9	BIPB1-4,6-10	HISA 1,2,7-8		HISA 6	HISA 3,9	HISA 10	HISA 4	HISB 1,3	HISB 6	HISB 2	HISB 4,7,9
	Antigen Library CDR1 CDR2 CDR3 CDR1 CDR2 CDR3	Antigen Library CDR1 CDR2 CDR3 CDR1 CDR3 CDR3 CDR3 9 Bovine Primary SYAMS <u>IIGSEGWPTI</u> YADSVKG <u>GGSM</u> FDY RASQSISSYLN <u>RASS</u> LQS QQ <u>SSNTPY</u> T ubiquitin NNK	Antigen Library CDR1 CDR2 CDR3 CDR1 CDR3 CDR3 CDR3 CDR3 Bovine Primary SYAMS IIGSEGWPTIYADSVKG GGSMFDY RASQSISSYLN RASSLQS QQSSNTPYT ubiquitin NNK "SomaticNNK AYAMT AISGSGGSTYYADSVKG KASSFDY RASQSISSYLN AASSLQS QQSYSTPST	Antigen Library CDR1 CDR2 CDR3 CDR3 CDR1 CDR2 CDR3  Bovine Primary  "SomaticNNK AYAMT AISGSGGSTYYADSVKG KASSFDY RASQSISSYLN RASGISSYLN RASSLQS  "RASQSISSYLN RASSLQS QQSYSTPST  "RASBIP PrimaryNNK SYAMS LISPLGKDTSYADSVKG RAGIFDY RASQSISSYLN HASRLQS QQYRLRPLT	1-9 Bovine Primary SYAMS IIGSEGWPTIYADSVKG GGSMFDY RASQSISSYLN RASGSISSYLN RAS	S Antigen Library CDR1 CDR2 CDR3 CDR1 CDR3 CDR1 CDR2 CDR3 CDR3 CDR3 CDR3 CDR3 CDR3 CDR3 CDR3	sAntigenLibraryCDR1CDR2CDR3CDR1CDR3CDR3CDR3CDR31-9Bovine ubiquitin 1,3-10 3,6,9Primary RABIP 1SomaticNNK NX 1A1SGSGGSTYYADSVKG 1KASSFDY 	sAntigenLibraryCDR1CDR2CDR3CDR1CDR2CDR31-9Bovine ubiquitin 1,3-10   "Primary   "SomaticNNK   "AISGGGSTYYADSVKG   "KASSFDY   RASQSISSYLN   RASQSISSYLN   RASQSISSYLN   RASQSISSYLN   RASQSISSYLN   "AASSLQS   WASQSISSYLN   WASQSISSY	sAntigenLibraryCDR1CDR2CDR3CDR1CDR3CDR3CDR3CDR3CDR31-9BovinePrimarySYAMSIIGSEGWPTIYADSVKGKASSFDYRASQSISSYLMRASSLQSQQSSNTPYT1,3-10"SomaticNNKAYAMIAISGSGGSTYYADSVKGRAGIFDYRASQSISSYLMHASRLQSQQSYSTPET3,6,9RatBIPPrimaryMNKSYAMSLISPLGKDTSYADSVKGGGRLFDYRASQSISSYLMYASHLQSQQSYSTPYT7,9"SYAMSAINTKGMTTDYADSVKGGSQAFDYRASQSISSYLMAASSLQSQQSYSTPYT4,6-10"SomaticNNKNYQMHAISGSGGSTYYADSVKGGTRRFDYRASQSISSYLMAASSLQSQQSYSTPYT1,2,7-8BovinePrimaryMNKSYAMSAISPKGRRTYYADSVKGRDKLFDYRASQSISSYLMBASSLQSQQSYSTPYT1,2,7-8BovinePrimaryMNKSYAMSAISPKGRRTYYADSVKGRDKLFDYRASQSISSYLMBASSLQSQQSYSTPYT1,2,7-8BovinePrimaryMNKSYAMSAISPKGRRTYYADSVKGRDKLFDYRASQSISSYLMBASSLQSQQSYSTPYT	S	1-9         Bovine ubiquitin         Frimary         SYAMS         IGSEGMETIYADSVKG         GGSMFDY         RASQSISSYLN         GASSLQS         CDR3           1,3-10         "biquitin         NNK         AISGSGGSTYYADSVKG         KASSETSYLN         RASQSISSYLN         AASSLQS         QOSYSTPET           3,6,9         RatBIP         PrimaryNNK         SYAMS         IISPIGKDTSYADSVKG         RAGGIFDY         RASQSISSYLN         HASBLQS         QOSYSTPET           7,9-6-10         "         "         SYAMS         AINTKGMTTDYADSVKG         GGRLFDY         RASQSISSYLN         AASSLQS         QOSYNIKPET           4,6-10         "         SOmaticNNK         NYQMH         AISGSGGSTYYADSVKG         GTRRFDY         RASQSISSYLN         AASSLQS         QOSYNIKPET           1,2,7-8         Bovine         PrimaryNNK         SYAMS         AISBKGRRTTYADSVKG         RDKLFDY         RASQSISSYLN         BASSLLQS         QOGGHRPIT           5         "         "         SYAMS         AITBAGRRTTYADSVKG         RDKLFDY         RASQSISSYLN         HASILQS         QOGGHRPIT           5         "         "         SYAMS         RITPAGHRTYADSVKG         RDKLFDY         RASQSISSYLN         HASILQS         QOGGHRPIT           5         "	Sample   Antigen   Library   CDR1   CDR2   CDR3   CDR3	Source   Library   CDR1   CDR2   CDR3   CD	South   Primary   SYAMS   11GSEGMPTIYADSVKG   GGSMFON   RASQSISSYLM   RASGLGS   CDR2   CDR2	Source   Primary   SYANG   IIGSEGNEPTIYADSVNG   GGSMFDY   RASQSISSYIN   RASGLGS   QOSSNEPET   Alsone   Primary   SYANG   IIGSEGNEPTIYADSVNG   GGRLFDY   RASQSISSYIN   RASGLGS   QOSTREPET   Alsone   PrimaryNWK   SYANG   IISPEGNETYADSVNG   GGRLFDY   RASQSISSYIN   Alsone   A	

FIG. 4A

PADOMEN AND
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7	$\sim$	$\leftarrow$	Υ	7	<del>,                                    </del>	4	7	$\vdash$	$\leftarrow$		$\vdash$	$\vdash$		$\vdash$	Н	$\vdash$	7	<b>←</b>	7	$\vdash$
QQSYSTPGT	QQSYRKPTT	QQGYRFPAT	QQ <u>SRNAPT</u> T	QQ <u>RSRP</u> P <u>A</u> T	QQSYSTPLT	QQSYSTPLT	QQSYSTPIT	QQSYSTPNT	QQSYSTPLT	QQRGGGPPT	QQSQRKPST	QQPRHMPQT	QQRHTNPPT	QQSKLSPVT	QQRSAGPLT	QQSYSTPRT	QQSYSTPRT	QH <u>PGLR</u> PGT	QQSDLPPST	QQSYSTPST
AASSLQS	HASALQS	RASTLOS	$\overline{R}AS\overline{R}LQS$	$\overline{\text{KAS}}\overline{\text{ILQS}}$	AASSLQS	AASSLQS	AASSLQS	AASSLQS	AASSLQS	AASRLQS	RASRLQS	RASRLQS	$\overline{\text{HASR}}$ LQS	NASRLQS	QASNLQS	AASSLQS	AASSLQS	RASRLQS	AASALQS	AASSLQS
RASQSILRTLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSIHSRLS	RASQSISSYLN	RASQSIQMGLS	RASQSISENLL	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSIRSRLS	RASQSIRTRLR	RASQSISSYLN	RASQSISSYLN	RASQSI <u>AKN</u> L <u>S</u>
GYRKFDY	GGLRFDY	RHKGFDY	GRYWFDY	SRRTFDY	RGLGFDY	RGMAFDY	ARWRFDY	TPRPFDY	TPRPFDY	KSQHFDY	TAPPFDY	RRAGFDY	RSFRFDY	TYPKFDY	SAKAFDY	RTFRFDY	KTGMFDY	<u>YLHT</u> FDY	YLHTFDY	RPSTFDY
AISGSGGSTYYADSVKG	RIPARGTVTHYADSVKG	GISHTGSNTRYADSVKG	RIAPEGGRTKYADSVKG	<u>TISYLGEKTR</u> YADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG	<u>TISPYGKQ</u> TRYADSVKG	TITPRGSLTSYADSVKG	GISAYGTVTYYADSVKG	SITNSGLATAYADSVKG	GITTRGQTTRYADSVKG	TIPARGGHTKYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG	AINRRGSATRYADSVKG	AINRRGSATRYADSVKG	AISGSGGSTYYADSVKG
RYRMG	SYAMS	SYAMS	SYAMS	SYAMS	RYGMH	SYRMV	KYNMH	RYRMH	RYRMH	SYAMS	SYAMS	SYAMS	SYAMS	SYAMS	SYAMS	MYRMG	SYAMT	SYAMS	SYAMS	RYRMW
=	NIP-BSA PrimaryNNK	"		=	SomaticNNK	"		=	"	FITC-BSA PrimaryNNK	H		=	ıı.	#	SomaticNNK	=	PrimaryNNK	=	SomaticNNK
=	NIP-BSA	ш	z	=	=	×	H	×	×	FITC-BSA	H	=	=	E	=	=	<b>11</b>	Human leptin	=	E
HISB5,8	NIPA2,7,10	NIPA3	NIPA5, 6, 9	NIPA1,8	NIPB1	NIPB2-4,7	NIPB5,6	NIPB8	NIPB9	10CG1	10CG2	10CG3	10CG5	10CG6	10CG7	10DH1	10DH2,3	11061	110G2,3	11DH2

FIG. 4B

Н 2	η κ	$\vdash$	$\vdash$	$\vdash$	Н	1		m	7	7	П	П	1	$\leftarrow$
QQSYSTP <u>S</u> T QQ <u>RAGT</u> P <u>V</u> T	QQ <u>RVLRPP</u> T QQSYSTP <u>H</u> T	QQNRTAPRT	QQSDTSPTT	QQ <u>MRRKPA</u> T	QQSYSTPKT	QQSYSTPIT	QQSYSTPRT	QQ <u>RKRL</u> P <u>E</u> T	QQSYSTPRT	QQSDSSPYT	QQSYSTPNT	QQLGTPPRT	$\overline{Q}$	QQSYSTP <u>N</u> T
AASSLQS <u>S</u> AS <u>R</u> LQS	<u>Q</u> AS <u>R</u> LQS AASSLQS	RASHLQS	YASNLQS	TASRLQS	AASSLQS	AASSLQS	AASSLQS	NASTLQS	AASSLQS	DASSLQS	AASSLQS	SASTIOS	AASSLQS	AASSLQS
RASQSI <u>KQR</u> LH RASQSISSYLN	RASQSISSYLN RASQSI <u>VRV</u> L <u>T</u>	RASQSISSYLN	RASQSISSYLN	RASQSISSYLN	RASQSI <u>SKS</u> LI	RASQSI $\overline{\mathrm{DRYLN}}$	RASQSIKYNLA	RASQSISSYLN	RASQSIHQDLV	RASQSISSYLN	RASQSIGSSLS	RASQSISSYLN	RASQSIFTNLD	$ ext{RASQSI}\overline{ ext{GTLLR}}$
RPSTFDY NIRIFDY	NISMIFDY GFYAFDY	NHSTFDY	GYYTFDY	NADLFDY	EWSRFDY	THDSFDY	HLSRFDY	SGKHFDY	PFMSFDY	GYYSFDY	DGAGFDY	GYSRFDY	SWTLFDY	SWTLFDY
AISGSGGSTYYADSVKG <u>SIAPAGRH</u> TYYADSVKG	GITMTGRTTKYADSVKG AISGSGGSTYYADSVKG	TITASGPNTRYADSVKG	TI YYAGSNTYYADSVKG	MIYPGGY-TKYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG	EILPRGHRTAYADSVKG	AISGSGGSTYYADSVKG	SIGSSGYGTGYADSVKG	AISGSGGSTYYADSVKG	AISGLGKQTRYADSVKG	AISGSGGSTYYADSVKG	AISGSGGSTYYADSVKG
"  RYRMW  Primery NNK SYAMS in	" SYAMS Somatic NNK RYPMS	Primary NNK SYAMS	PrimaryDVT SYAMS	Primary NNK SYAMS	Somatic NNK $\underline{LYNMV}$	<u>GYYMS</u>	" $RYQMV$	Primary NNK SYAMS	Somatic NNK YYEML	Primary DVT SYAMS	$Somatic\ DVT\ \underline{ ext{DYDMS}}$	Primary NNK SYAMS	Somatic NNK RYEMS	" RYEMS
" Human Pr thyroglobulin	3 " "	BSA	==	H		=	н	14CG1,2,3 Hen egg lysozyme	11	Mouse 1gG	=	Human 1gG	11	=
11DH3 12CG1,2	12CG3 " 12DH1,2,3 "	13061	13CG2	13063	13DH1	13DH2	13DH3	14CG1,2,	14DH2,3	19CG1,3	19DH2	20CG1	20DH1	20DH2

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 $\star$  of clone sequenced



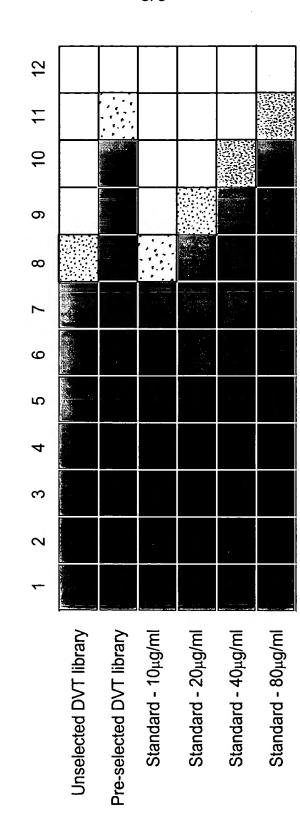


FIG. 5A

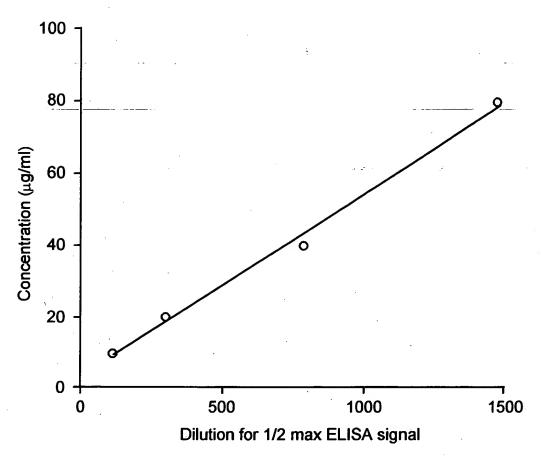


FIG. 5B

